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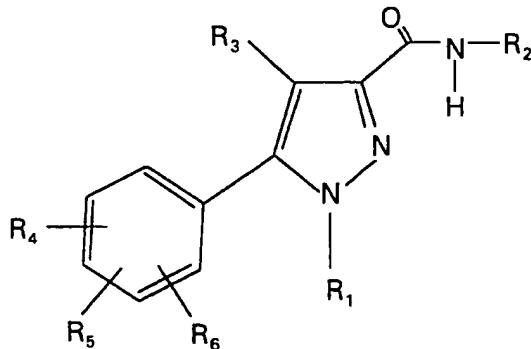
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(54) Title: PYRAZOLE DERIVATIVES AS CANNABINOID RECEPTOR ANTAGONISTS

(57) Abstract: Novel cannabimimetic pyrazole derivatives are presented which have preferentially high affinities for both of the cannabinoid CB1 or CB2 receptor sites. The improved receptor affinity makes these analogs useful as experimental tools for cannabinoid receptor studies as well as clinically useful agents in individuals and animals for treatment of memory deficits associated with aging or neurological diseases, as anti-obesity agents, as medications for schizophrenia and treatment of septic shock syndrome.

**What Is Claimed Is:**

## 1. A compound of the formula



or a physiologically acceptable salt thereof, wherein:

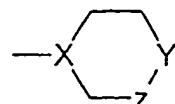
R<sub>1</sub> is a branched or unbranched chain having the structure (CH<sub>2</sub>)<sub>n</sub>Z where n is an integer from 1 to about 10 and Z is selected from the group consisting of H, halogen, N<sub>3</sub>, NCS, CN, OH, OCH<sub>3</sub>, NH<sub>2</sub> and CH=CH<sub>2</sub>;

R<sub>3</sub> is selected from the group consisting of H and a branched or unbranched chain having the structure (CH<sub>2</sub>)<sub>n</sub>CH<sub>3</sub> where n is an integer from 0 to about 3;

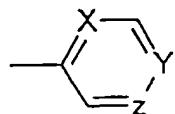
R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are each selected from the group consisting of halogen, N<sub>3</sub>, NCS, OCH<sub>3</sub>, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, NO<sub>2</sub>, NH<sub>2</sub>, phenyl and phenyl with at least one substituent from the group consisting of halogen, N<sub>3</sub>, NCS, OCH<sub>3</sub>, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, NO<sub>2</sub>, and NH<sub>2</sub>; and

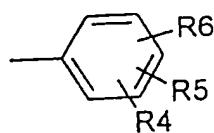
R<sub>2</sub> is selected from the group consisting of naphthyl,

where X is selected from the group consisting of N and CH and Y and Z are each selected from the group consisting of O, N, S and (CH<sub>2</sub>)<sub>n</sub> where n is an integer from 1 to about 7,

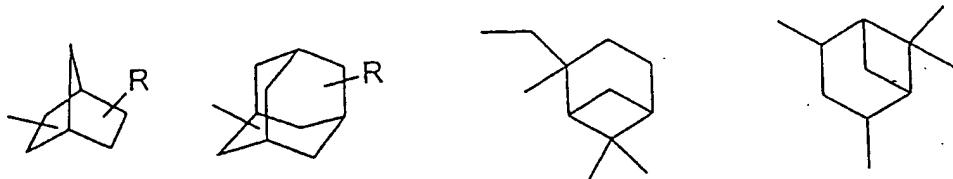


where X, Y and Z are each selected from the group consisting of N and CH,



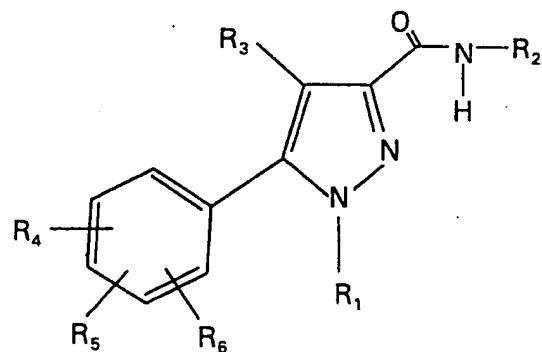


where  $R_4$ ,  $R_5$  and  $R_6$  are each selected from the group consisting of halogen,  $N_3$ , NCS,  $OCH_3$ ,  $CH_3$ ,  $CH_2CH_3$ ,  $NO_2$ ,  $NH_2$  and phenyl,



where  $R$  is selected from the group consisting of H, halogen,  $N_3$ , NCS, CN, OH,  $OCH_3$ ,  $NH_2$  and  $CH=CH_2$ .

2. A method of preferentially binding to the cannabinoid receptors in an individual or animal comprising administering to the individual or animal a therapeutically effective amount of a compound having the formula

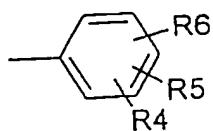


and physiologically acceptable salts thereof, wherein:

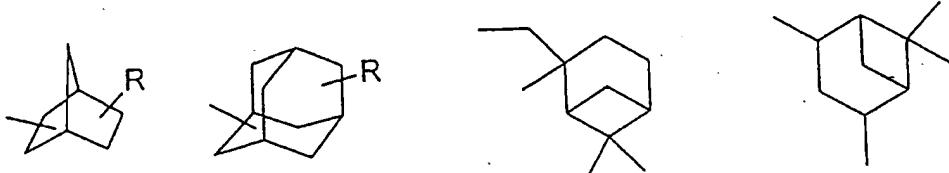
$R_1$  is a branched or unbranched chain having the structure  $(CH_2)_nZ$  where  $n$  is an integer from 1 to about 10 and  $Z$  is selected from the group consisting of H, halogen,  $N_3$ , NCS, CN, OH,  $OCH_3$ ,  $NH_2$  and  $CH=CH_2$ ;

$R_3$  is selected from the group consisting of H and a branched or unbranched chain having the structure  $(CH_2)_nCH_3$  where  $n$  is an integer from 0 to about 3;

$R_4$ ,  $R_5$  and  $R_6$  are each selected from the group consisting of halogen,

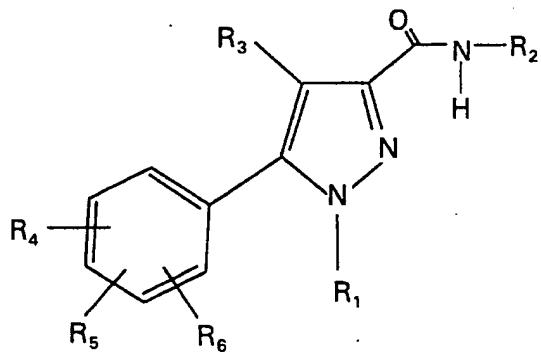


where  $R_4$ ,  $R_5$  and  $R_6$  are each selected from the group consisting of halogen,  $N_3$ , NCS,  $OCH_3$ ,  $CH_3$ ,  $CH_2CH_3$ ,  $NO_2$ ,  $NH_2$  and phenyl,



where  $R$  is selected from the group consisting of H, halogen,  $N_3$ , NCS, CN, OH,  $OCH_3$ ,  $NH_2$  and  $CH=CH_2$ .

2. A method of preferentially binding to the cannabinoid receptors in an individual or animal comprising administering to the individual or animal a therapeutically effective amount of a compound having the formula



and physiologically acceptable salts thereof, wherein:

$R_1$  is a branched or unbranched chain having the structure  $(CH_2)_nZ$  where  $n$  is an integer from 1 to about 10 and  $Z$  is selected from the group consisting of H, halogen,  $N_3$ , NCS, CN, OH,  $OCH_3$ ,  $NH_2$  and  $CH=CH_2$ ;

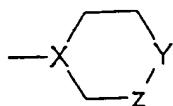
$R_3$  is selected from the group consisting of H and a branched or unbranched chain having the structure  $(CH_2)_nCH_3$  where  $n$  is an integer from 0 to about 3;

$R_4$ ,  $R_5$  and  $R_6$  are each selected from the group consisting of halogen,

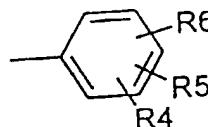
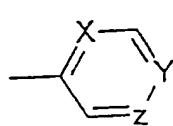
$\text{N}_3$ ,  $\text{NCS}$ ,  $\text{OCH}_3$ ,  $\text{CH}_3$ ,  $\text{CH}_2\text{CH}_3$ ,  $\text{NO}_2$ ,  $\text{NH}_2$ , phenyl and phenyl with at least one substituent from the group consisting of halogen,  $\text{N}_3$ ,  $\text{NCS}$ ,  $\text{OCH}_3$ ,  $\text{CH}_3$ ,  $\text{CH}_2\text{CH}_3$ ,  $\text{NO}_2$ , and  $\text{NH}_2$ ; and

$\text{R}_2$  is selected from the group consisting of napthyl,

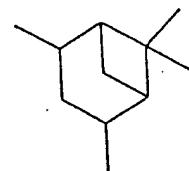
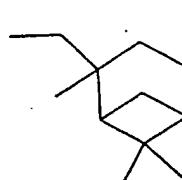
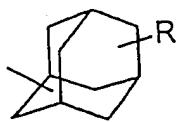
where  $\text{X}$  is selected from the group consisting of  $\text{N}$  and  $\text{CH}$  and  $\text{Y}$  and  $\text{Z}$  are each selected from the group consisting of  $\text{O}$ ,  $\text{N}$ ,  $\text{S}$  and  $(\text{CH}_2)_n$  where  $n$  is an integer from 1 to about 7,



where  $\text{X}$ ,  $\text{Y}$  and  $\text{Z}$  are each selected from the group consisting of  $\text{N}$  and  $\text{CH}$ ,

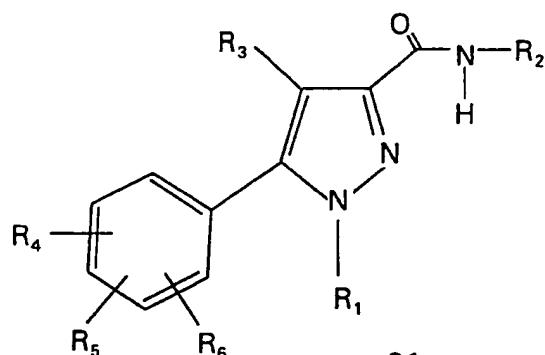


where  $\text{R}_4$ ,  $\text{R}_5$  and  $\text{R}_6$  are each selected from the group consisting of halogen,  $\text{N}_3$ ,  $\text{NCS}$ ,  $\text{OCH}_3$ ,  $\text{CH}_3$ ,  $\text{CH}_2\text{CH}_3$ ,  $\text{NO}_2$ ,  $\text{NH}_2$ , phenyl and



where  $\text{R}$  is selected from the group consisting of  $\text{H}$ , halogen,  $\text{N}_3$ ,  $\text{NCS}$ ,  $\text{CN}$ ,  $\text{OH}$ ,  $\text{OCH}_3$ ,  $\text{NH}_2$  and  $\text{CH}=\text{CH}_2$ .

3. A pharmaceutical composition containing a therapeutically effective amount of a compound having the formula



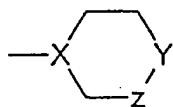
and physiologically acceptable salts thereof, wherein:

$R_1$  is a branched or unbranched chain having the structure  $(CH_2)_nZ$  where  $n$  is an integer from 1 to about 10 and  $Z$  is selected from the group consisting of H, halogen,  $N_3$ , NCS, CN, OH,  $OCH_3$ ,  $NH_2$  and  $CH=CH_2$ ;

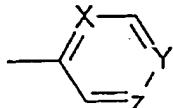
$R_3$  is selected from the group consisting of H and a branched or unbranched chain having the structure  $(CH_2)_nCH_3$  where  $n$  is an integer from 0 to about 3;

$R_4$ ,  $R_5$  and  $R_6$  are each selected from the group consisting of halogen,  $N_3$ , NCS,  $OCH_3$ ,  $CH_3$ ,  $CH_2CH_3$ ,  $NO_2$ ,  $NH_2$ , phenyl and phenyl with at least one substituent from the group consisting of halogen,  $N_3$ , NCS,  $OCH_3$ ,  $CH_3$ ,  $CH_2CH_3$ ,  $NO_2$ , and  $NH_2$ ; and

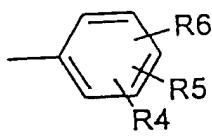
$R_2$  is selected from the group consisting of napthyl,



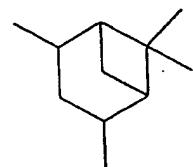
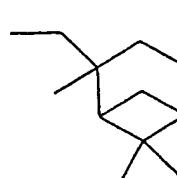
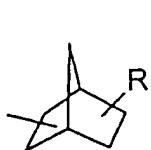
where  $X$  is selected from the group consisting of N and CH and Y and Z are each selected from the group consisting of O, N, S and  $(CH_2)_n$  where  $n$  is an integer from 1 to about 7,



where  $X$ ,  $Y$  and  $Z$  are each selected from the group consisting of N and CH,



where  $R_4$ ,  $R_5$  and  $R_6$  are each selected from the group consisting of halogen,  $N_3$ , NCS,  $OCH_3$ ,  $CH_3$ ,  $CH_2CH_3$ ,  $NO_2$ ,  $NH_2$ , phenyl and



where  $R$  is selected from the group consisting of H, halogen,  $N_3$ , NCS, CN, OH,  $OCH_3$ ,  $NH_2$  and  $CH=CH_2$ .